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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/340,664	11/16/1994	KAARE M. GAUTVIK	FORSK3.0001	5529

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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/340,664	GAUTVIK ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31 and 33-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31 and 33-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/7/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 31 and 33-42 are pending and under consideration.

The rejection of claims 33-35 under 35 U.S.C. §102(b) as anticipated or obvious over Brewer has been overcome by the amendments to the claims.

New rejections apply.

The declaration by Dr. Gautvik submitted 8/11/2004 has been fully considered to the following effect:

At paragraph 3, declarant asserts that the isolated hPTH described in the Brewer '132 patent was less than 90% pure. Declarant asserts at paragraphs 4 and 7 that Brewer made three amino acid errors in the sequence. At paragraph 7, declarant asserts that the "probable conclusion" as to why Brewer's sequence contained three errors was that the final hPTH preparation was impure. This argument has been fully considered but is not deemed persuasive because it is merely conjecture, and is not supported by fact or evidence. Brewer sequenced 34 amino acids. By declarant's own statement, three were in error. However, this means that the other 31 were correct. It is *not* probable that there were serious contaminants present, as Brewer had a greater than 90% accuracy rate. If there were serious contaminants, one would expect that Brewer would have been unable to obtain any sequence. If the errors were the result of serious contamination, it is not likely that Brewer would have correctly identified 31 of the 34 residues. A more parsimonious explanation is that the three errors are merely the result of the reduced accuracy that is a feature of amino acid sequencing, as explained by Declarant at paragraph 8. Further, at paragraph 10, declarant clearly states that "typically, sequencing mistakes start to occur after the first 15-20 amino acids in the peptide are analyzed by Edmond degredations". This is consistent with the result obtained by Brewer, the errors having occurred at residues 22, 28 and 30. Accordingly, the presence of 'serious contaminants' appears to be declarant's opinion, and is not supported by fact or evidence. The evidence of record, which is supported by the declaration, indicates that Brewer had a preparation that was sufficiently homogeneous so as to be sequenceable, that three errors were made in sequencing, that the presence of those three errors is consistent with what is known about the technique used (as characterized by Declarant),

and that the protein of Brewer was, in fact, of the same sequence as applicant's hPTH1-84, the sole differences being due to the aforementioned errors. Declarant's conclusion at the end of paragraph 11 that "The fact that the hPTH sequence disclosed by Brewer in Figure 1 contains 3 mistakes suggests that Brewer's final hPTH preparation contained contaminants and is clearly less than 90% pure" is a non-sequiteur, as there is no connection made between the three errors and a specific percentage of purity, and is further not supported by fact or evidence, and appears to be declarant's opinion.

Declarant's discussion pertaining to acceptable standards and the lack of 'genuine chromatograms' is not persuasive, as it is an attempt to cast aspersions on the Brewer patent, and is not fact or evidence.

At paragraph 12, declarant states that gas chromatography, one of the methods used by Brewer to analyze the residues being sequenced, "is known to cause separation difficulties with several amino acid residues", including the three mistakenly identified by Brewer. This statement supports the Examiner's finding that the mistakes were *not* due to impurities in Brewer's preparation, but rather were well-known difficulties with the technique being used. The supposition that Brewer *could* have used other techniques is not relevant.

At paragraphs 14-16, Declarant argues that Brewer started with a "less than recommended amount of hPTH for sequencing", and that it is "unlikely" that Brewer could have isolated 3.15 mg of hPTH from parathyroid gland adenomas that was more than 90% pure. This argument has been fully considered but is not deemed persuasive because (a) the amount of material used by Brewer is not relevant to the rejection at hand; the fact that Brewer had a preparation of hPTH that meets the limitations of the claims is. Declarant's own arguments support the hypothesis that Brewer's preparation was pure, as declarant has provided persuasive reasons *other than protein impurities* for the three erroneously identified amino acids. Declarant's argument and conclusion that "It would be impossible for a skilled artisan to purify 3.15 mg of hPTH from 16 glands" appears to be declarant's opinion only, and is not supported by fact or evidence. It is long established that since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural

and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Declarant's opinions doe not meet this burden.

The declaration by Dr. Gautvik submitted 10/7/2004 has been fully considered to the following effect:

The stated purpose of the declaration is to show that the impurities of the commercial preparations used as hPTH standards in the specification result in decreased PTH activity. As there are no activity limitations in the claims, the declaration addresses a property which is not at issue, and is not persuasive in overcoming the rejection over the standards used by applicants in the specification.

Rejections over Prior Art

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 36-42 are rejected under 35 U.S.C. § 102(b) as anticipated by Brewer et al., U.S. Patent Number 3,886,132 as applied to claims 31 and 32 in the Examiner Answer mailed 7/28/2000, and as affirmed by the Board of Patent Appeals and Interferences (BPAI) in the decision mailed July 2, 2003. Also note the discussion of the two Gautvik declarations, above.

Claims 31 and 33-34 are rejected under 35 U.S.C. § 102(b) as being unpatentable over Breyel et al. (3rd Eur. Cong. Biotech., cited by appellants) or Mayer et al. (EP 0 139 076, cited by appellants).

Breyel et al. teach expression of mature hPTH in *E. coli*, see Summary, page 363. The protein was expressed and bacterial cell extracts assayed for activity, see page 366 for example. Said extracts would inherently be free of human derived proteins and human infections agents.

Mayer et al. teach recombinant production of hPTH in *E. coli*, see page 9, first full paragraph for example, page 12 of the enclosed English-language translation. The protein was purified from the cells and shown to be biologically active. The preparation of Mayer et al. would inherently be free of human derived proteins and human infections agents.

Claims 31 and 33-35 are rejected under 35 U.S.C. 102 (a), (b) and/or (f) as being anticipated over applicant's admission of the prior art.

As noted by the BPAI at page 12 of the decision of 7/2/2003, the specification at page 7 teaches the use of an hPTH standard (1-84) to compare and assess the results of the purification process. The specification teaches that the purification product eluted in the same peak as this standard and comigrated with the standard as one band on a gel. The specification implicitly asserts that these comparisons demonstrate the purity and completeness of the protein being claimed. In order for the "standard" to have been useful for such comparison, it itself must have met the limitations of the pending claims. It is further noted that the standards, which are by applicants characterization "synthetic", would inherently not contain human derived proteins or infectious agents. Applicants arguments of this rejection have been fully considered but are not deemed persuasive. Applicants argue at page 12 of the response that all of the synthetic PHT preparations "necessarily contain chemically modified amino acids, such as protecting groups, resulting from the chemical processes used to make the compounds. This argument has been fully considered but is not deemed persuasive because while protecting groups are used in the process of synthesis, they must be removed to attach subsequent residues. Applicant's assertion

that all synthetic peptides must contain chemically modified amino acids is simply not true, and is not supported by fact or evidence.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 36-42 are rejected under 35 U.S.C. 102 (a), (b) and/or (f) as being anticipated, of in the alternative, under 35 U.S.C. § 103 as obvious over by applicants admission of the prior art for reasons of record with respect to claims 31 and 33-35.

The Gautvik declaration of 10/7/2004 is noted. Therein, it is disclosed that the commercial preparations were not 100% pure, but rather contained impurities. Therefore, the Examiner is not able to determine whether or not the preparations were 90% pure. Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Claim 35 remains rejected under 35 U.S.C. § 103 as being unpatentable over Breyel et al. (3rd Eur. Cong. Biotech., cited by appellants) or Mayer et al. (EP 0 139 076, cited by appellants), any reference of the three in view of Kaisha et al. (GB 2 092 596, cited by appellants), and Brewer et al., U.S. Patent Number 3,886,132.

Applicants have traversed that one could not use the purification method of Brewer could not be used on the proteins of Breyel or Meyer. This argument has been fully considered but is not deemed persuasive because (a) it is not supported by fact or evidence, and (b) it ignores the skill level of the ordinary artisan. The person of ordinary skill in the art would be easily able to adapt Brewer's method to the bacterial isolates of Breyel or Meyer. The presence of shorter peptides would in no way interfere with the process. Further, applicant's supposition that there would be no such shorter peptides in a sample of hPTH from parathyroid tissue ignores basic biology, which would teach that one would indeed expect partially degraded peptides *in vivo*, as well as cleaved peptides, as it is normal for hPTH 1-84 to be cleaved to produce hPTH 1-34 and 35-84 *in vivo*. Therefore, applicant's argument is at odds with what is known about hPTH; see for example, U.S. Patent Number 4,508,828, at column 1. There is no evidence of record that hPTH 1-84 would be the only form found in dried, defatted parathyroid tissue, nor that the presence of other forms would complicate the purification method of Brewer. Applicant's argument that chromatographic separation of hPTH from fragments of same would be difficult has been fully considered but is not deemed persuasive. Brewer purified the protein by gel filtration, and ion exchange chromatography, both methods that separate proteins by *size*, among other properties; see for example figure 5.2 of Scopes "Protein Purification: principles and practice, Springer-Verlag, NY, 1982. Once again, applicant's argument is at odds with the science involved.

Finally, applicants argue at page 15 of the response filed 10/7/2004 that the protein of Breyel is *not* mature hPTH 1-84, and point to publications by Hogset and Kareem in support of their argument. This argument has been fully considered but is not deemed persuasive. Breyel specifically describes the protein produced as "mature human parathyroid hormone (1-84 AA), see abstract. Hogset states that "the major excreted product is correctly processed human identical hPTH (1-84) (abstract). There is no statement in Hogset that the protein of Breyel was

otherwise. Breyel did not use the Protein A signal sequence, nor mutations thereof as disclosed by Kareem et al., such that the significance of the Kareem publications is not clear to the Examiner.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Lindall et al., U.S. Patent Number 4,508,828, disclose immunoaffinity purification of hPTH. See claims, for example.

Sindrey et al., U.S. Patent Number 5,208,041 disclose and claim essentially pure human parathyroid hormone.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner